ical manifestations of the disease usually occur after the period of reproduction, although not in the atypical case described elsewhere in this issue of the journal.[5] It has also been postulated that a modest increase in the efficiency of iron absorption in heterozygotes might represent a countervailing positive feature, analogous to the protective effect of heterozygous sickle-cell trait against falciparum malaria.

The clinical manifestations of hemochromatosis vary widely and may be subtle.[1,2] Clearly, physicians must not wait for the appearance of bronzed diabetes with cirrhosis before the diagnosis is considered. If 1 of every 300 to 400 white patients seen in a hospital, clinic, or office has hemochromatosis, the diagnosis is more frequently missed than made. It is true that the full disease does not develop in carriers of the disorder and that women, who are genetically hemochromatotic as frequently as are men, much more rarely accumulate sufficient iron for clinical manifestations to develop (in one study only about 15% of women with genetic hemochromatosis were clinically affected). Menstrual periods and pregnancies allow for substantial iron loss and serve to protect against iron overload. In fact, when clinical hemochromatosis does appear in women, it is usually after menopause. As a result, its manifestations tend to occur later in women than in men.

Weakness, lethargy, abdominal pain, seronegative arthritis, impotence, and glucose intolerance are some of the nonspecific early manifestations of hemochromatosis. How can the diagnosis be made then? The disease must be suspected much more frequently than has been customary in the past. In the absence of a means to detect the abnormal gene itself, we are currently confined to studying the time-delayed phenotypic expression of the disease, that of iron overload. For practical purposes, iron overload (especially greater than 4 grams) in the absence of excessive transfusions, or more rarely, prolonged enhanced erythropoiesis, is almost always due to hemochromatosis. When the diagnosis is made in a patient, it can then be traced in his (more rarely, her) family by HLA linkage analysis. At present, the transferrin saturation test has proved to be the most useful test for detecting iron overload.[6] Other tests are described elsewhere.

Therapy is simple and effective if the diagnosis is made before severe liver disease or the destruction of pancreatic islet beta cells occurs. A hemochromatotic gut slowly but inappropriately pumps iron into the body; a phlebotomist can rapidly pump it out. Removing 500 ml of whole blood removes 200 to 250 mg of iron. Heme itself is the ideal chelator. A weekly phlebotomy can therefore remove 10 to 12 grams of iron per year, which may represent the accumulation of two decades. The genetic defect remains, but its adverse effect can be easily obviated if an early diagnosis is made. Even when the diagnosis is delayed, heart failure and abnormal liver function may be reversed, and even glucose tolerance may improve.

Hemochromatosis is both prevalent and insidious. We must consider this diagnosis much more frequently because genetic "pumping iron" leads to organ destruction, not to body building.

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Advances in Diagnosing and Managing Pituitary Adenomas

IN THE PAST DECADE we have seen a tremendous increase in knowledge regarding the pathogenesis, diagnosis, and management of pituitary tumors, as summarized by Aron and colleagues in this issue of the journal.[1] Their review reflects the experience of a major academic center for pituitary tumor research. What salient points can be gleaned from this experience and from other recent advances?

First, pituitary lesions are not rare. Magnetic resonance (MR) imaging reveals focal pituitary hypointensities in as many as 40% of healthy persons.[2] Most of these are small microadenomas or other benign lesions, but macroadenomas are occasionally found when patients undergo computed tomographic or MR scanning for unrelated indications. How should cases of pituitary mass lesions be evaluated?

To answer this question, it is helpful to review the clinical effects of pituitary adenomas. Pituitary tumors usually present with some combination of three syndromes: symptoms due to the mass itself, symptoms due to a disruption of normal pituitary function, and symptoms due to the oversecretion of pituitary hormones. The first two syndromes depend on the size of the tumor, and the third can occur with small lesions. Therefore, patients with large lesions require formal visual field examination and assessment of normal pituitary function, whereas all patients require assessment of excess hormone secretion.

What is the appropriate biochemical assessment of pituitary function in patients with pituitary mass lesions? There is no single answer to this question, but recent discoveries provide some guidelines:

• *Prolactin oversecretion*: Prolactinomas are the most common pituitary tumor and, in general, are the only ade-

noma type that can be treated medically. Therefore, a serum prolactin measurement should be done in all patients with pituitary mass lesions. Not all patients with hyperprolactinemia and a pituitary tumor have a prolactinoma; any large tumor can cause mild prolactin elevations. *Undersecretion*: Prolactin deficiency is not routinely evaluated or treated.

• *Growth hormone oversecretion*: Some tumors that secrete growth hormone do not cause clinical acromegaly and are mistaken for nonfunctioning tumors.[3] Therefore, a random insulin-like growth factor I (IGF-I) level is helpful in patients with macroadenomas as a marker for excess growth hormone secretion. (IGF-I is produced by the liver under the influence of growth hormone, and its measurement is a better screening test than a random growth hormone level.) *Undersecretion*: Patients are not currently screened for growth hormone deficiency because exogenous growth hormone is not routinely given to adults with a growth hormone deficiency. This recommendation may change, however, depending on results from ongoing trials.[4]

• *Corticotropin (adrenocorticotropic hormone) oversecretion*: A 24-hour urinary free cortisol level is the best screening test for suspected Cushing's syndrome. The further evaluation of such cases is difficult, and patients should be referred to centers where corticotropin-releasing hormone tests and inferior petrosal sinus sampling are available.[5] Most patients with Cushing's disease have microadenomas, and radiologic studies should not be done until the biochemical diagnosis of Cushing's syndrome is assured. *Undersecretion*: If a patient with a macroadenoma is scheduled for a surgical procedure, screening for corticotropin deficiency may not be necessary because the patient will require reexamination postoperatively. If preoperative adrenal insufficiency is suspected, short-term glucocorticoid therapy can be prescribed through the time of the operation. If a surgical procedure is not planned, a corticotropin (cosyntropin [Cortrosyn])-stimulation test can be done to rule out adrenal insufficiency.

• *Thyrotropin (thyroid-stimulating hormone) oversecretion*: Thyrotropin-secreting tumors are rare, and patients with this disorder present with hyperthyroidism. A clue to their presence is a nonsuppressed thyrotropin level (using one of the new sensitive immunometric assays) in a patient with thyrotoxicosis. *Undersecretion*: Free thyroxine (T_4) and thyrotropin levels are sufficient to evaluate the thyroid axis in patients with macroadenomas. Of note, many patients with central hypothyroidism have "normal" thyrotropin levels, although these levels are inappropriate for the low free T_4 levels.[6] Therefore, a thyrotropin level alone can be misleading in evaluating for pituitary tumors.

• *Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) oversecretion*: Until recently, gonadotropin tumors were thought to be rare because they produce no typical clinical syndrome. It is now clear, however, that most clinically nonfunctioning tumors—which constitute 30% of all pituitary adenomas—are in fact gonadotropin-producing.[7] Therefore, in patients with macroadenomas, serum LH and FSH levels should be measured—with a serum testosterone or estradiol level—as tumor markers. *Undersecretion*: Serum LH, FSH, and sex steroid levels are adequate to evaluate the normal gonadal axis in patients with macroadenomas.

• *α-Subunit oversecretion*: Thyrotropin, LH, and FSH are each composed of an α- and a β-subunit. Many pituitary tumors secrete excess amounts of uncombined α-subunit, alone or with other hormones.[7] Although the α-subunit has no bioactivity, it is a helpful tumor marker, and its levels should be measured in patients with macroadenomas. *Undersecretion*: Deficiency of the α-subunit has no clinical effects and does not require evaluation.

Once a patient with a pituitary tumor has been evaluated according to the above guidelines, treatment options must be weighed. Therapy is obviously tailored for each patient, but the following broad guidelines are to be kept in mind:

• *Surgery*: The treatment of choice for most symptomatic pituitary tumors is transsphenoidal surgical excision (with the exception of prolactinomas). Surgical success rates are dependent on surgical skill and experience; the remission rates achieved by Aron and co-workers are difficult to match in community practice. Therefore, patients should be referred to neurosurgeons with an active interest in pituitary tumors.

The issue of remission rates following surgical therapy is especially important for patients with prolactinomas because these tumors can be treated medically. Aron and co-workers report 75% long-term surgical success rates for prolactin microadenomas, with lower success rates for macroadenomas. Other centers report long-term surgical remission rates as low as 40% for prolactin microadenomas and 6% to 29% for macroadenomas.[8-12] Based on these figures, many experts recommend that patients with prolactinomas receive medical, rather than surgical, therapy.

• *Radiation therapy*: Radiation therapy has long been used as primary or adjuvant treatment of pituitary tumors. The gradual development of hypopituitarism is an accepted side effect, but long-term neuropsychiatric effects have not been clarified. Therefore, despite suboptimal surgical cure rates for macroadenomas, many experts withhold postoperative radiation therapy in patients with clinically nonfunctioning tumors. Tumor regrowth may not become a clinical problem within a patient's lifetime, and tumor recurrence can often be treated by repeated transsphenoidal adenomectomy. Radiation therapy remains a useful postoperative treatment of secretory tumors that continue to cause clinical problems due to hormone excess.

• *Medical therapy*: Medical therapy for pituitary tumors, nonexistent 20 years ago, is now commonplace for the following tumor types:

Prolactinomas. In the view of many experts, the dopamine agonist bromocriptine hydrochloride is the treatment of choice for prolactinomas of any size. In most

patients, bromocriptine therapy decreases serum prolactin levels, improves pituitary function, and reduces tumor size, with none of the side effects of surgical therapy.[13] The optimal duration of bromocriptine treatment is unclear. Some women with microadenomas have remission of hyperprolactinemia, so therapy can be discontinued in these patients after one or two years, with close monitoring for recurrence.[14] In contrast, most patients with macroadenomas require permanent bromocriptine therapy.[15]

What are the medical options for patients who are not helped by bromocriptine therapy?[13] Other dopamine agonists may be effective; pergolide mesylate is marketed in the United States (although not approved for the treatment of prolactinomas), but other dopamine agonists are in clinical trials. Vaginal bromocriptine administration is an option for women who have side effects with oral bromocriptine. Finally, women with prolactin microadenomas who do not desire fertility can safely receive oral contraceptives or estrogen replacement therapy, which treat the estrogen-deficiency state without causing tumor growth.[16]

Acromegaly. The use of the somatostatin analogue octreotide decreases growth hormone levels in most patients with acromegaly. But it causes tumor shrinkage in only a few patients. Therefore, it is most useful in patients who cannot undergo a surgical procedure or who have persistent disease postoperatively.

Cushing's disease. As reviewed by Aron and coworkers, the results of the medical treatment of Cushing's disease remain disappointing.

Thyrotropin-secreting tumors. Octreotide is useful as adjuvant therapy for reducing excess thyrotropin secretion, although its effects on tumor size are variable.

Gonadotropin and α-subunit tumors. Currently no effective medical therapy is available for these tumors. Recent trials suggest, however, that the administration of gonadotropin-releasing hormone antagonists may prove useful as adjuvant therapy.[17]

- *Observation*: Patients with nonfunctioning microadenomas can be observed without therapy, with follow-up scanning to rule out tumor growth. Patients with nonfunctioning macroadenomas should undergo surgical resection or, if completely asymptomatic, should be observed closely with scanning.[18]

Finally, what can recent advances in molecular biology teach us about the pathogenesis of pituitary adenomas? Although molecular studies suggest that pituitary adenomas are monoclonal in origin, specific genetic abnormalities have been identified only in a few tumors. A loss of chromosome sequences that contain the putative *MEN1* tumor suppressor gene has been reported in a subset of growth hormone-secreting adenomas, whereas activating mutations in the *Gs* α-subunit gene have been found in various functioning and nonfunctioning adenomas.[19] Future studies of such genetic alterations may present new opportunities for the diagnosis and treatment of pituitary tumors.

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